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Modelling of Glucose-Insulin-Glucagon Pharmacodynamics in Man

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***Abstract*— The purpose is to build a simulation model of the glucoregulatory system in man. We estimate individual human parameters of a physiological glucose-insulin-glucagon model. We report posterior probability distributions and correlations of model parameters.**

I. Introduction

In healthy individuals, insulin and glucagon work in a complex fashion to maintain blood glucose levels within a narrow range. Recent studies suggest a multiplicative effect of insulin and of glucagon on endogenous glucose production (EGP) [1].

II. Materials and Methods

A. PD Model

The pharmacodynamics (PD) model is mainly inspired by Hovorka et al. [2].

$$\dot{Q}_1(t) = -F_{01} - S_T x_1(t) Q_1(t) + k_{12} Q_2(t) + F_{IC}(t) \quad (1a)$$

$$\dot{Q}_2(t) = S_T x_1(t) Q_1(t) - (k_{12} + S_D x_2(t))\, Q_2(t) \quad (1b)$$

$$\dot{x}_i(t) = k_i\,(I(t) - x_i(t)) \qquad i = 1, 2, 3 \quad (1c)$$

$Q_1(t)$ and $Q_2(t)$ are the masses of glucose per bodyweight (μmol/kg) in the accessible and non-accessible compartments. Glucose concentration (mmol/L) in the accessible compartment is $Q_1(t)/\mathrm{V}$ with V fixed at 160 mL/kg. $I(t)$ is the insulin concentration (mIU/L) in the accessible compartment. $x_i(t)$ are the remote effects of insulin (mIU/L).
F_{01} is the non-insulin-dependent glucose flux. k_{12} and k_i are transfer rate constants. S_D, S_E, and S_T are insulin sensitivities.
The model in (1) is modified so $F_{IC}(t)$ is the insulin and glucagon dependent EGP [3].

$$F_{IC}(t) = \frac{(1 - S_E x_3(t))}{(1 - S_E \mathrm{I}_{b,y})} \cdot \left((E_{max} - \mathrm{E}_0) \frac{C(t)}{C_{E50} + C(t)} \right) \quad (2)$$

$C(t)$ is the glucagon concentration (pg/mL) in the accessible compartment. $\mathrm{I}_{b,y}$ is the fixed basal insulin concentration (mIU/L) for subject y, and E_0 is the minimum EGP fixed at 8 μmol/(kg·min). E_{max} is the maximum EGP at $I_{b,y}$. C_{E50} is the glucagon concentration at half maximum EGP.

B. Parameter Estimation

We used maximum a posteriori to estimate PD model parameters and profile likelihood analysis to reduce unidentifiable parameters in data with measurements of glucose, insulin and glucagon from ten healthy male subjects who received a 1 mg subcutaneous bolus of marketed glucagon.

III. Results

TABLE I

Posterior distributions of parameters across population.

Parameter	Unit	Mean	SD
C_{E50}	pg/mL	407	39
E_{max}	μmol/(kg·min)	38.8	5.0
F_{01}	μmol/(kg·min)	10.5	0.95
$\ln(k_{12})$	min^{-1}	-3.48	0.26
$\ln(k_2)$	min^{-1}	-2.11	0.03
$\ln(k_3)$	min^{-1}	-4.20	0.74
$\ln(S_E)$	per mIU/L	-3.19	0.67
$\ln(S_T)$	min^{-1} per mIU/L	-5.73	0.54
$\ln(k_1)$	min^{-1}	-5.69	*
$\ln(S_D)$	min^{-1} per mIU/L	-7.58	*

* Fixed unidentifiable parameter.

TABLE II

Posterior correlation matrix of identifiable parameters.

	C_{E50}	E_{max}	F_{01}	$k_{12}*$	k_2*	k_3*	S_E*	S_T*	BW
C_{E50}	1								
E_{max}	0.31	1							
F_{01}	0.32	-0.30	1						
$k_{12}*$	0.45	0.23	0.22	1					
k_2*	-0.63	0.06	-0.13	-0.30	1				
k_3*	0.13	-0.34	0.82	-0.02	-0.33	1			
S_E*	-0.82	-0.26	-0.40	-0.22	0.43	-0.35	1		
S_T*	-0.20	-0.22	-0.13	0.45	-0.28	-0.14	0.57	1	
BW	0.61	-0.43	0.39	0.24	-0.70	0.42	-0.60	0.00	1

* Correlation of ln-transformed parameter.

IV. Conclusions

The model enables simulations of the glucose-insulin-glucagon dynamics in man at the following concentrations: glucagon (180-8000 pg/mL), insulin (1.2-81.9 mIU/L) and glucose (3.3-11.5 mmol/L).

References

[1] A. Emami *et al.*, "Modelling glucagon action in patients with type 1 diabetes," *J-BHI*, 2016, submitted.

[2] R. Hovorka *et al.*, "Partitioning glucose distribution/transport, disposal, and endogenous production during IVGTT," *Am J Physiol Endocrinol Metab*, vol. 282, no. 5, pp. E992–E1007, 2002.

[3] S. L. Wendt *et al.*, "PK/PD modeling of glucose-insulin-glucagon dynamics in healthy dogs after a subcutaneous bolus administration of native glucagon or a novel glucagon analogue," DTU Compute, Tech. Rep. 2016-2, 2016.

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